APPLICANT'S REMARKS

Claims 1–3 and 9–14 are pending and currently amended. Claims 6–8 are withdrawn. Claims 4 and 5 are canceled.

1. Rejection of claims 1–3 and 9–14 under 35 U.S.C. 112, 2nd paragraph

Claims 1–3 and 9–14 have been rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite.

Concerning claims 1–3, the Examiner asserts that the phrase "slightly soluble salt" renders the claims indefinite because "the specification does not provide a standard for ascertaining the requisite degree."

The Applicant respectfully disagrees with the Examiner and submits that the definition of "slightly soluble salts" is clearly set forth in the present specification and makes clear the boundaries of the subject matter for which protection is sought.

The present specification as published states at paragraph 12:

> "Slightly soluble salts" for the purposes of the invention have a solubility in water of less than 0.1, preferably less than 0.01,% by weight based on water at 25° C. and a pH of 7. Such slightly soluble salts include C_{16}-C_{18} fatty acid salts of the betaine (III) and salts of the betaine (III) with acids such as, for example, the

embonates or else salts of the betaine (III) with bases such as N,N'-dibenzylethylenediamine.

Therefore, the Applicant respectfully requests reconsideration and withdraw of the rejection of claims 1–3 based on 35 U.S.C. 112, 2nd paragraph.

Concerning claims 1 and 14, the Examiner asserts that the phrase "solid betaine of the formula III" renders those claims indefinite because it is unclear if the claims define a "betaine salt."

The Applicant respectfully disagrees with the Examiner and submits that one skilled in the art would clearly understand that the betaine of formula III is a salt-forming compound and, moreover, that the term "betaine" designates a base form, *i.e.*, a non-salt form.

From the structure of formula III *per se*, as well as the specification and claims, one skilled in the art would understand that formula III is not itself a salt form and must be a salt-forming compound. For example, the structure of formula III as recited in the present claims does not indicate either positively or negatively charged ions. Furthermore, Formula III cannot already be a salt form because claim 1 further recites "a slightly soluble salt" of formula III and several dependent claims recite the embonate and hemiembonate salts of formula III.

Moreover, for the sake of clarity and precision, the present specification and claims recite the word "betaine" to clearly designate the base form of ciprofloxacin and/or enrofloxacin. "Betaine" is an art-recognized word for the base form of ciprofloxacin and enrofloxacin (*see,*

e.g., CIPRO XR package insert submitted with the accompanying I.D.S.). Unfortunately, as is evident from the cited references, the word "ciprofloxacin" alone is often used to designate ciprofloxacin hydrochloride. So as to avoid any inconsistencies with the prior art, the present claims recite the art-recognized term "betaine" to designate the base form of ciprofloxacin or enrofloxacin (in contrast to an acid salt form thereof, *e.g.*, ciprofloxacin hydrochloride).

Therefore, the Applicant respectfully requests reconsideration and withdraw of the rejection of claims 1 and 14 based on 35 U.S.C. 112, 2nd paragraph.

2. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 102(e) based on PILKEIWICZ

Claims 1, 2, and 14 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Published Patent Application No. 2004/0009126 (PILKIEWICZ). The Examiner asserts that PILKEIWICZ teaches a method of treating bacterial lung infection comprising local administration of ciprofloxacin by inhalation, wherein the ciprofloxacin is in the form of particles and may be in the form of dry powder.

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not anticipated by PILKEIWICZ because, for example, PILKEIWICZ only teaches a water-soluble form of ciprofloxacin entrapped in liposomes, which is clearly distinguishable from the insoluble betaines recited by the current claims.

The making of liposomal ciprofloxacin is described in Example 2 of PILKIEWICZ at paragraphs 72 to 74. According to PILKIEWICZ, a 16 mg/ml "stock Cipro solution" was used to made liposomal ciprofloxacin (paragraph 73). The "stock Cipro solution," at 16 mg of ciprofloxacin per ml of water, is a solution comprising a water-soluble form of ciprofloxacin, such as, perhaps, ciprofloxacin hydrochloride.

The Applicant respectfully submits that PILKIEWICZ, in fact, does not indicate any reason for using an insoluble form of ciprofloxacin. PILKIEWICZ does not contemplate using an insoluble form of ciprofloxacin, or even suggest that using an insoluble form of ciprofloxacin might be possible.

According to PILKIEWICZ at paragraph 59:

> As shown in FIG. 2, liposomal ciprofloxacin administered intratracheally is maintained at a high level in the lungs for two hours whereas the lung levels of free ciprofloxacin delivered intratracheally were negligible after one hour…Thus liposomal ciprofloxacin given by inhalation is more advantageous with respect to targeting and retention in the lung than free ciprofloxacin given either by inhalation or orally.

These test results are also discussed at paragraph 74.

Therefore, one skilled in the art, reading PILKIEWICZ as a whole, would understand that a powder comprising liposomal-entrapped, water-soluble ciprofloxacin is superior to un-entrapped, water-soluble ciprofloxacin for delivery to the lungs as a treatment for intracellular infections.

Unlike PILKIEWICZ, independent claims 1 and 14 recite a method for controlling bacterial diseases of respiratory organs in humans and animals by locally administering an antibacterially effective amount of a solid betaine of the formula (III), wherein R is H or C_2H_5, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension. When R is H, the betaine of formula III is ciprofloxacin betaine. When R is C_2H_5, the betaine of formula III is enrofloxacin betaine.

Ciprofloxacin betaine and enrofloxacin betaine are bases, *i.e.*, non-salt forms that are quite insoluble in water. For example, the solubility of ciprofloxacin betaine in water is less than about 0.1 mg/ml (*see* CAÇO et al. submitted with the accompanying I.D.S.) These betaines may be transformed into slightly soluble salts, such as mono-embonate or hemi-embonate salts. As discussed hereinabove, the phrase "slightly soluble" is defined by the present specification as: a solubility in water at 25°C of less than 0.1% by weight.

Therefore, PILKIEWICZ does not teach or even suggest all the features of the invention as recited in claims 1, 2, and 14. Accordingly, the Applicant respectfully submits that the 35 U.S.C. 102(e) rejection of claims 1, 2, and 14 based on PILKIEWICZ should be reconsidered and withdrawn.

3. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 103(a) based on MAYER and LI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER et al., *Clinical Presentation of Inhalation Anthrax Following Bioterrorism Exposure*, in view of LI et al., *Ciprofloxacin-loaded bovine serum albumin microspheres: preparation and drug release* in vitro. The Examiner argues that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a dry powder inhaler for delivery of a ciprofloxacin composition of LI directly to the respiratory track for treatment of a respiratory track bacterial infection.

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not obvious based on the combination of MEYER and LI. Even assuming, *arguendo*, that the references were properly combined, the cited combination does not provide or even suggest the features of the invention recited in claims 1, 2, and 14.

Specifically, the cited combination does not provide or even suggest a method for controlling bacterial diseases of the respiratory organs in humans and animals by locally administering an antibacterially effective amount of a solid ciprofloxacin betaine or enrofloxacin betaine, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension.

MEYER is cited only for the proposition that ciprofloxacin is useful to treat bacterial infections in the lungs (*i.e.*, inhalational anthrax). MEYER, as acknowledged by the Examiner, does not

teach the local administration of an antibiotic, but rather parental administration. Also, the particular ciprofloxacin formulation used by MEYER is undisclosed.

LI does provide a ciprofloxacin formulation that may be administrated to the lungs by dry powder inhalation. The composition of LI is bovine serum albumin microspheres produced with a water-soluble form of ciprofloxacin (page 826, Experimental). Specially, LI dissolves ciprofloxacin in distilled water to which BSA is added before the aqueous solution was spray dried. BSA becomes the biodegradable wall material entrapping the aqueous solution of ciprofloxacin.

The Applicant respectfully submits that LI, in fact, does not indicate any reason for using an insoluble form of ciprofloxacin. LI does not contemplate using an insoluble form of ciprofloxacin, or even suggest that using an insoluble form of ciprofloxacin might be possible.

Unlike the cited combination of MEYER and LI, the present independent claims 1 and 14 recite a method for controlling bacterial diseases of the respiratory organs in humans and animals by locally administering an antibacterially effective amount of a solid ciprofloxacin betaine or enrofloxacin betaine, or a solid slightly soluble salt thereof, in a powder form or powder-containing suspension.

Again, ciprofloxacin betaine and enrofloxacin betaine are bases, *i.e.*, non-salt forms that are only slightly soluble in water. These betaines may be transformed into slightly soluble salts, such as

ciprofloxacin mono-embonate or ciprofloxacin hemi-embonate. The phrase "slightly soluble" is defined by the present application as: a solubility in water at 25°C of less than 0.1% by weight.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on MAYER and LI.

4. Rejection of Claims 3 and 9–13 under 35 U.S.C. 103(a) based on MEYER, LI, GROHE, and VETTER

Claims 3 and 9–13 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER and LI, and further in view of U.S. Patent No. 4, 670,444 (GROHE) and U.S. Patent No. 5,808,076 (VETTER).

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not obvious based on MEYER, LI, GROHE, and VETTER.

Even assuming, *arguendo*, that the cited references are properly combined, the resulting combination of references does not provide or even suggest the invention recited in dependent claims 3 and 9–13. Specifically, the combination of cited references does not provide embonate and/or hemiembonate salts of ciprofloxacin betaine or enrofloxacin betaine in a powder form or powder-containing suspension for local administration to control bacterial diseases of respiratory organs in humans and animals.

As discussed hereinabove, the combination of MEYER and LI does not provide or even suggest ciprofloxacin betaine or enrofloxacin betaine or salts thereof in a powder form or powder containing suspension that is locally administered to control bacterial diseases of the respiratory organs in humans and animals. Combining MEYER and LI with GROHE and VETTER does not cure these deficiencies.

GROHE, in Example 23, teaches ciprofloxacin hydrochloride monohydrate obtained as colorless crystals. Example 24 of GROHE teaches enrofloxacin hydroiodide. The Applicant respectfully submits that GROHE does not teach or even suggest the betaine salts as presently recited in claims 3 and 9–13. GROHE also does not teach or suggest such betaine salts in a powder form or powder-containing suspension. Neither does GROHE teach or even suggest ciprofloxacin and/or enrofloxacin betaine salts for local administration.

The betaine salts as presently recited in claims 3 and 9–13 is also not provided by VETTER, which reference teaches the mixture of a quinolone acid (*e.g.*, ciprofloxacin or enrofloxacin) or a salt thereof with embonic acid or a salt thereof. According to VETTER, in the final mixture, the molar ratio of the quinolone acid to embonic acid can be 1:0.5 to 1:5. In other words, the quinolone acid and embonic acid are separate components of the final mixture. The Applicant respectfully submits that an embonate salt of the compound of formula III is not merely the mixture of a quinolone acid and embonic acid (or a salt thereof).

Therefore, the Applicant respectfully submits that the combination of MEYER, LI, GROHE, and VETTER does not teach or even suggest all the feature of the invention recited by claims 3 and

9–13. The Applicant respectfully requests that the 35 U.S.C. 103(a) rejection of claims 3 and 9–14 based on MAYER, LI, GROHE, and VETTER be reconsidered and withdrawn.

5. Rejection of Claims 1, 2, and 14 under 35 U.S.C. 103(a) based on PILKIEWICZ and KANIKANTI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over PILKIEWICZ in view of U.S. Pub. Pat. App. No. 2004/0024018 (KANIKANTI). The Examiner argues that one skilled in the art at the time of the invention would have combined ciprofloxacin betaine (as provided by KANIKANTI) with the PILKIEWICZ method.

The Applicant respectfully disagrees with the Examiner and submits that the references are not properly combined. First, attempting to combine the insoluble ciprofloxacin betaine of KANIKANTI with the liposomes of PILKIEWICZ would change the basic principle of operation of PILKIEWICZ. As discussed above, PILKIEWICZ teaches liposomal formulations of water-soluble ciprofloxacin. In contrast, ciprofloxacin betaine of KANIKANTI is the slightly soluble base form of ciprofloxacin. Second, one skilled in the art would have no expectation that PILKIEWICZ could be successfully combined with KANIKANTI. PILKIEWICZ gives no reason to use an insoluble form of ciprofloxacin of KANIKANTI or even suggest that it could be possible to use an insoluble form of ciprofloxacin.

The Applicant respectfully requests that the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on PILKIEWICZ and KANIKANTI be reconsidered and withdrawn.

6. Rejection of Claims 1, 2, 14 under 35 U.S.C. 103(a) based on MEYER, LI, and KANIKANTI

Claims 1, 2, and 14 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER and LI, and further in view of KANIKANTI.

The Applicant respectfully disagrees with the Examiner and submits that the references are not properly combined. First, attempting to combine the insoluble ciprofloxacin betaine of KANIKANTI with the microspheres of LI would change the basic principle of operation of LI. As discussed above, LI teaches microsphere formulations of water-soluble ciprofloxacin. In contrast, ciprofloxacin betaine of KANIKANTI is the slightly soluble base form of ciprofloxacin. Second, one skilled in the art would have no expectation that LI could be successfully combined with KANIKANTI. LI gives no reason to use an insoluble form of ciprofloxacin of KANIKANTI or even suggest that it could be possible to use an insoluble form of ciprofloxacin.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the 35 U.S.C. 103(a) rejection of claims 1, 2, and 14 based on MAYER, LI, and KANIKANTI.

7. Rejection of Claims 3 and 9–13 under 35 U.S.C. 103(a) based on MEYER, LI, GROHE, VETTER, and KANIKANTI

Claims 3 and 9–13 were rejected under 35 U.S.C. 103(a) as being unpatentable over MAYER, LI, GROHE, VETTER, and KANIKANTI.

The Applicant respectfully disagrees with the Examiner and asserts that the present claims are not obvious based on MAYER, LI, GROHE, VETTER, and KANIKANTI.

The Applicant respectfully disagrees with the Examiner and submits that the references are not properly combined. First, attempting to combine the insoluble ciprofloxacin betaine of KANIKANTI with the microspheres of LI would change the basic principle of operation of LI. As discussed above, LI teaches microsphere formulations of water-soluble ciprofloxacin. In contrast, ciprofloxacin betaine of KANIKANTI is the slightly soluble base form of ciprofloxacin. Second, one skilled in the art would have no expectation that LI could be successfully combined with KANIKANTI. LI gives no reason to use an insoluble form of ciprofloxacin of KANIKANTI or even suggest that it could be possible to use an insoluble form of ciprofloxacin.

Even assuming, *arguendo*, that the cited references are properly combined, the resulting combination of references does not provide or even suggest the invention recited in dependent claims 3 and 9–13. Specifically, the combination of cited references does not provide embonate and/or hemiembonate salts of ciprofloxacin betaine or enrofloxacin betaine in a powder form or powder-containing suspension for local administration to control bacterial diseases of respiratory organs in humans and animals.

As discussed hereinabove, the combination of MEYER, LI, GROHE, and VETTER does not provide or even suggest all the feature of the invention recited by claims 3 and 9–13. KANIKANTI does not cure the deficiencies of MEYER, LI, GROHE, and VETTER because KANIKANTI is completely silent concerning the present claimed embonate and/or hemiembonate salts of ciprofloxacin betaine and/or enrofloxacin betaine.

In light of the foregoing, the Applicant respectfully requests reconsideration and withdraw of the 35 U.S.C. 103(a) rejection of claims 3 and 9–14 based on MAYER, LI, GROHE, VETTER, and KANIKANTI.

8. Conclusion

The Applicant respectfully requests favorable consideration and that this application be allowed.

Respectfully submitted,

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